the blood contact side, the formation of a confluent monolayer ensues by the cells growing under a permanent influence of defined pulsatile shear forces increasing up to physiological values, by means of streaming the prosthesis surface on the blood contact side along a main axis of the prosthesis in an inner perfusion circuit [[and]] or by moistening an outer prosthesis wall in an outer perfusion circuit, or in a permeable medium reservoir.

2. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, characterized in that the increasing shear forces are generated by means of a program-controlled pumping device (7).

3. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, characterized in that the mathematical value of the increasing shear forces can be selected variably and time-independently.

4. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, characterized in that the mathematical value and the final value of the shear forces can be selected freely and time-variably by means of a program control according to the physiological conditions of the implantation location.

5. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, characterized in that the mathematical value of the occurring shear forces can be

adjusted by varying pumping capacity, as well as by varying the size of the cross-section of pumping tubes used or of any other connecting elements outside of [[the]] a chamber, as well as by the geometrical form and configuration of the very chamber.

6. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, produced by means of a perfusion circuit consisting of an inner perfusion circuit (5) for streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis inside of [[the]] a chamber (2), said prosthesis (1) being fixed in the inner space thereof by means of adapters (3, 3'), and hence constituting as such the inner perfusion circuit (5), and an outer perfusion circuit (5') for outwardly streaming the prosthesis (1) within the same chamber (2) which comprises, towards the outside, connections to a pumping device (7) for both circuits (5, 5'), as well as to the permeable medium ~~reservoirs~~ reservoir (6, 6') which also have the function of pressure equation reservoirs.

7. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, produced by means of a perfusion circuit consisting of an inner perfusion circuit (5) for streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis inside of [[the]] a chamber (2), said prosthesis (1) being fixed in the inner space thereof by means of an adapter (3), and hence constituting as

such the inner perfusion circuit (5), and an outer perfusion circuit (5') uniting inside of the chamber (2) with the inner perfusion circuit (5) after having streamed the prosthesis (1) for outwardly streaming the prosthesis (1) within the same chamber (2) which comprises, towards the outside, connectors to a pumping device (7) for both circuits (5, 5'), as well as to the permeable medium reservoir ~~reservoirs~~ (6, 6') which also have the function of pressure equation reservoir.

8. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that the outer perfusion circuit (5') can be operated by a method selected from the group consisting of co-current transporting to the inner perfusion circuit (5), counter-current transporting to the inner perfusion circuit (5), and static transporting to the inner perfusion circuit (5).

9. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that the perfusion circuits lead from one medium reservoir (6) into another medium reservoir (6'), in which the medium collected has already streamed through the prosthesis.

10. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that the inner and the outer perfusion circuits have different medium reservoirs or one and the same medium reservoir (6, 6').

11. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that the prosthesis is present in the [[very]] permeable medium reservoir, and that the inner and the outer perfusion circuits are thereby connected with each ~~another~~ other.

12. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that the medium reservoirs are comprised of expandable blood bags of the materials PVC or EVAM.

13. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that ~~the realization of~~ the adapters (3, 3') for fixing the prosthesis (1) ~~is realized~~ are furnished by an olive .

14. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, ~~characterized in that~~ wherein the prothesis is to be clamped and wherein a [[the]] length of the prosthesis ~~to be clamped~~ can be varied by constructionally providing at least one closing part with the adapter (3 or 3') of chamber (2).

15. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that the chamber (2) is manufactured from a transparent material.

16. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 1, characterized in that the prosthesis is used as a member selected from the group consisting of a vascular prosthesis, a heart valve prosthesis and a stent.

17. (currently amended) Method for covering cardiovascular ~~prostheses~~ prothesis with endothelial cells according to claim 1, characterized in that after an initial sub-confluent seeding of the prosthesis surface on the blood contact side, the formation of a confluent monolayer ensues by the cells growing under permanent influence of defined pulsatile shear forces increasing up to physiological values by means of streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis in an inner perfusion circuit, [[and]] or a moistening of the outer prosthesis wall in an outer perfusion circuit or in a permeable medium reservoir.

18. (currently amended) The method according to claim 17, characterized in that

a) the increasing shear forces are generated by means of a program-controlled pumping device (7),

b) the mathematical value of the increasing shear forces can be selected variably and time-independently,

c) the mathematical value and the final value of the shear forces can be selected freely and time-variably by a program control according to the physiological conditions of the implantation location, and

d) the mathematical value of the arising shear forces can be adjusted by varying the pumping capacity, as well as by varying the size of the cross-section of [[the]] pumping tubes used or of any other connecting elements outside of [[the]] a chamber, as well as by the geometrical form and configuration of the very chamber.

19. (previously presented) The method according to claim 17 characterized in that in an inner perfusion circuit (5) for streaming through the inner prosthesis space along the main axis of the prosthesis inside of the chamber (2), the prosthesis (1) is fixed by means of adapters (3, 3'), and hence as such constitutes the inner perfusion circuit (5), and that an outer perfusion circuit (5') exists for outwardly streaming the prosthesis (1) in the same chamber (2) which, towards the outside, comprises for the two circuits (5, 5') connectors to a pumping device (7) and medium reservoirs (6, 6') which also have the function of pressure equation reservoirs.

20. (currently amended) The method according to claim 17, characterized in that

[[a)]] the outer perfusion circuit (5') can be operated in a way selected from the group consisting of co-current to the inner perfusion circuit, [[or]] counter-current to the inner perfusion circuit (5), ~~but also~~ and statically,

[[b)]] the two perfusion circuits (5, 5') do not work as a closed system but lead from one medium reservoir (6) into another medium reservoir (6'), in which the medium collected has already streamed through the prosthesis,

~~c) the inner and the outer perfusion circuits have a member selected of the group consisting of different medium reservoirs and one and the same medium reservoir (6, 6'),~~ and

[[d)]] the two perfusion circuits (5, 5') unite inside the chamber (2) after having streamed the prosthesis (1), but leave the chamber (2) in separate perfusion circuits (5, 5').

21. (currently amended) The method according to claim 17, characterized in that the prosthesis is present in the [[very]] permeable medium reservoir and that the inner and the outer perfusion circuits are thereby connected with each other ~~another~~.

22. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that ~~the realization of~~ the adapters (3, 3') for fixing the prosthesis (1) ~~is realized~~ are furnished by cones with clamping means.

23. (currently amended) Cardiovascular ~~prostheses~~ prothesis according to claim 6, characterized in that ~~the realization of~~ the adapters (3, 3') for fixing the prosthesis (1) ~~is realized~~ are furnished by an expansion member.

24. (currently amended) Cardiovascular ~~prostheses~~ prothesis comprising an endothelial cell surface produced wherein the formation of a confluent monolayer ensues by the cells growing under a permanent influence of defined pulsatile shear forces increasing up to physiological values after an initial sub-confluent seeding of a surface on the blood contact side, by means of streaming the prosthesis surface on the blood contact side along a main axis of the prosthesis in an inner perfusion circuit [[and]] or by moistening an outer prosthesis wall in an outer perfusion circuit, or in a permeable medium reservoir.

25. (currently amended) The cardiovascular ~~prostheses~~ prothesis according to claim 24 wherein the shear force is from about 0.01 to 5 dyn/cm2.

26. (previously presented) The cardiovascular ~~prostheses~~ prothesis according to claim 24 wherein a confluent endothelial layer having a high quality is present.

27. (currently amended) A method for covering cardiovascular ~~prostheses~~ prothesis with endothelial cells comprising the following steps:
initially sub-confluently seeding the prosthesis surface on the blood contact side;

streaming the prosthesis surface on the blood contact side along the main axis of the prosthesis in an inner perfusion circuit, [[and]] or a moistening of the outer prosthesis wall in an outer perfusion circuit or in a permeable medium reservoir;

growing cells growing under a permanent influence of defined pulsatile shear force increasing up to physiological values;

forming a confluent monolayer of the grown cells.

28. (currently amended) The method for covering cardiovascular prostheses according to claim 27 further comprising employing a shear force from about 0.01 to 5 dyn/cm2.

29. (currently amended) The method for covering cardiovascular ~~prostheses~~ prothesis according to claim 27 further comprising forming a confluent endothelial layer having a high quality.

30. (currently amended) The method for covering cardiovascular ~~prostheses~~ prothesis according to claim 27 further comprising

varying pumping capacity of endothelial cells for adjusting the size of occurring shear forces.

31. (currently amended) The method for covering cardiovascular ~~prostheses~~ prothesis according to claim 27 further comprising

generating increasing shear forces by means of a program-controlled pumping device (7).

32. (new) The method according to claim 17, characterized in that

the outer perfusion circuit (5') can be operated in a way selected from the group consisting of co-current to the inner perfusion circuit (5), counter-current to the inner perfusion circuit (5), and statically,

the inner and the outer perfusion circuits have a member selected of the group consisting of different medium reservoirs and one and the same medium reservoir (6, 6'), and

the two perfusion circuits (5, 5') unite inside the chamber (2) after having streamed the prosthesis (1), but leave the chamber (2) in separate perfusion circuits (5, 5').

REMARKS

Claims 1 through 31 continue to be in the case.

New claim32 is being introduced.

New claim 32 is based on the language of claim 20.

Response to Amendment

1 The amendment filed *3/7/03* has been entered as Paper No. *7*. Changes to the abstract and Figures 1 and 2 have been approved by the examiner. The amendment filed *6/18/03* has been entered as Paper No. 10; new claim *30* has been added. The amendment filed *10/23/03* (first filed *4/24/03)* has been entered as Paper No. *12*. The changes to the claims have been approved by the examiner and new claims *23-29* have been added. The amendment filed *11/25/03* has been entered as Paper No. *13;* new claim *31* has been added. All pending claims, which are claims *1-31*, are being considered for further examination on the merits.

Applicant appreciates the approval of the drawing changes and the entry of the amendments.

The Office Action refers to Claim Objections 2. Claims *1-17* and *22-31* are objected to because of the following informalities: the preambles of the claims are to "cardiovascular prostheses" but the body of the claims makes reference to a prosthesis. The examiner suggests changing "cardiovascular prostheses" to --cardiovascular prosthesis-- so that the claim terminology is more consistent. Appropriate correction is required. *3.* Claims 11 and *21* are objected to because of the following informalities: on line *4* of both claims, it

appears that "another" should be changed to --other--. Appropriate correction is required.

Claims 1 to 17 and 21 to 31 are being corrected.

The Office Action refers to Claim Rejections - 35 USC § 112.

4. Claims 1-31 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and **distinctly claim** the subject matter which applicant regards as the invention.
5. Claims 1, 17, 24 and 27 are indefinite because it is unclear if the "permeable medium reservoir" is an alternative to both the inner and outer perfusion circuits, or if is an alternative to just the outer perfusion circuit. The "permeable medium reservoir" is an alternative to both the inner and outer perfusion circuits.
The two perfusion circuits (5, 5') can also work as a non-closed system. According to a further advantageous configuration, the two perfusion circuits (5, 5') lead from one medium reservoir (6) ibto another medium reservoir (6'), wherein the medium which has already flown through the prostasis is collected in the other medium reservoir (6'). Thereby the two perfusion circuits (5, 5') can be joined within the chamber (2) after having flown past the prothesis surface.
The inner and the outer perfusion circuit can have different reservoirs or one and the same medium reservoir (6, 6'). The prothesis can be present in the medium reservoir, and thereby, the inner and the outer perfusion circuit can be connected with one another.

6. Claim 5 recites the limitation "the chamber" in line 5. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 6 recites the limitations "the chamber" in line 4 and "the medium reservoirs" in line 10. There is insufficient antecedent basis for these limitations in the claim.

8. Claim 7 recites the limitations "the chamber" in line 4 and "the medium reservoirs" in line 11. There is insufficient antecedent basis for these limitations in the claim.

9. Claims 11 and 21 are indefinite because it is unclear what is meant by "the very medium reservoir".

10. Claims 13, 22 and 23 are indefinite because it is unclear what is meant by "the realization" and "realized"

11. Claim 14 recites the limitation "to be clamped" in line 2. There is insufficient antecedent basis for this limitation in the claim because the prosthesis is not required to be configured or adapted to be clamped and the process steps of the product claims 1 and 6, on which it depends, do not require clamping of the prosthesis.

12. Claim 18 recites the limitations "the pumping tubes" in line 3 of (d) and "the chamber" in line 4 of (d). There is insufficient antecedent basis for these limitations in the claim

13. Claim 20, part (a) is confusing and should be rewritten following the Markush format for listing of elements.

14. Claim 20 is indefinite because it is unclear how part (b) can require two separate reservoirs, and then part (c) require that the reservoirs are one and the same.

15. Claim 30 is indefinite because it is unclear of what the pumping capacity is being varied.

The applicant thanks the Examiner for the detailed observations and the present amendment furnishes corrections to overcome the rejections.

The Office Action refers to Claim Rejections - 35 USC § 102

17. Claims 1-31 stand rejected under 35 U.S.C. 102(a) as being anticipated by Dunkelman et al (WO 97/49799 as cited in applicant's IDS). Dunkelman et al. discloses a method for covering and cardiovascular prosthesis with endothelial cells with all the elements of claims 17-21 and 27-31. See Figure 4, page 3, lines 714, pages 7-8, lines 3-29 and page 11, lines 1-12 and pages 11-12, lines 28-3. The method includes apparatus comprising a chamber (46), pumping tube (58), adapters (33), cardiovascular prosthesis (26), reservoir (10), and pumping device (50). Because all of the method steps are met by Dunkelman et al., all of the structural limitations of the product claims of 1-16 and 22-26 are also met. A cardiovascular prosthesis has an initial sub-confluent seeding of endothelial cells on the surface thereof and then forms a confluent monolayer of endothelial cells.

Applicant respectfully disagrees.

The allegation in the Office Action that all structural elements of the claims 17 to 21 and 27 to 31 are found in the reference Dunkelman et al. (WO 97/49799) appears to be incorrect.

The shearing forces indicated in the reference Dunkelman et al. only have a small size value. Only a seeding covering a surface is possible with the shearing forces of the reference Dunkelman et al. An influence on the growth of the cells cannot be obtained with the shearing forces indicated by the reference Dunkelman et al. No growth of cells occurs therefore under shearing stress.

Claim 1 of the reference Dunkelman et al. reads;

" ... to cause the cells to become confluent and flatten ...."

This refers only to an adhering of the cells for reaching of a confluence, as is clearly shown and explained in the following example.:

The cell suspension is subdivided into four aliquots and is accordingly employed for times successively for coating. This multiple step procedure circumvents the risk of a non surface covering seeding. The circumvention of the reference Dunkelman et al. is again confirmed on page 8, where a description is furnished about the whereabouts of the fourth aliquot in the prothesis over night. However the incubation over night is described to be dispensible for production of a confluent mono layer in paragraph four of page 8 of the reference Dunkelman et al. This step of the reference Dunkelman et al. corresponds to an initial confluent settling, which settling excludes a growth of the cells and the shear stress in a proliferation method, wherein the shear stress is entered here only at a lower value and therewith a non-physiological value.

The reference Dunkelman et al says further to this point on page 8, paragraph 3 that a confluent, however not completely stable endothel cell mono layer is obtained with the above recited method of the reference Dunkelman et al., since partial cell disengagements occur.

Thus the claims of the present application are clearly distinguished from the reference Dunkelman et al.

The reference Dunkelman et al. does not teach the growth of endothel cells under the influence of shearing forces, wich increase up to physiological values. Consequently different products are obtained by the reference Dunkelman et al. as compared with the products claimed by the applicant.

Reconsideration of all outstanding rejections is respectfully requested.

All claims as presently submitted are deemed to be in form for allowance and an early notice of allowance is earnestly solicited.

Respectfully submitted,

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